11-27-96

DATA EVALUATION REPORT

KRESOXIM-METHYL

STUDY TYPE: SUBCHRONIC ORAL TOXICITY FEEDING - RAT (82-1a)

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by

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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity Feeding-Rat
OPPTS 870.3100 [§82-1a]
DP BARCODE: D225934
P.C. CODE: 129111
SUBMISSION CODE: S504279
TOX. CHEM. NO.: none

TEST MATERIAL (PURITY): Reg. No. 242 009 (KRESOXIM-METHYL) (98.7% w/w)

SYNONYMS: BAS 490F; alpha-(methoxyimino)-2-((2-methylphenoxy) methyl) benzeneacetic acid, methyl ester

CITATION: Mellert, W. (1994) Toxicology report. Subchronic toxicity with Reg. No. 242 009 (BAS 490F) in rats: Administration in the diet over 3 months. BASF Aktiengesellschaft Department of Toxicology, D-67056 Ludwigshafen/Rhine, FRG. BASF Registration Document No. 94/10954, Project No. 31S0577/90041, October 24, 1994. MRID 43864245. Unpublished.

Polloth, C. (1994) Toxicology Report. S-Phase Response with Reg. No. 242 009 in Rats After Administration in the Diet for 3 Weeks. BASF Aktiengesellschaft Department of Toxicology, D-67056 Ludwigshafen/Rhine, FRG. Report number 94/10922, October 5, 1994. MRID 43864246. Unpublished.

SPONSOR: BASF Corporation Agricultural Products Group, Research Triangle Park, NC 27709-3528.

EXECUTIVE SUMMARY: In a subchronic toxicity study (MRID 43864245) Reg. No. 242 009 (98.7% w/w, Lot #N 21) was administered to 10 Wistar rats/sex/dose in the diet at dose levels of 0, 500, 2000, 8000, or 16,000 ppm (0, 36, 146, 577, 1170 mg/kg/day for males and 0, 43, 172, 672, 1374 mg/kg/day for females, respectively) for 3 months.

All the animals survived to study termination. There were minor, statistically significant though not dose-related decreases in the body weights (≤ 9.5%, $p \leq 0.05$ or 0.01) and body weight gains (≤ 15.2%, $p \leq 0.05$) in 8000 and 16,000 ppm males. These were not accompanied by effects on food consumption or food efficiency. Gamma-glutamyl transferase (GGT) was elevated in males in a time and dose-dependent manner, reaching statistical significance at 8000 and 16,000 ppm on day 89 (about a 5-fold increase, $p \leq 0.01$). The only histopathological finding was a minor change in the amount and/or distribution of fat in hepatocytes (all dose groups, both sexes); it is unclear whether this effect is treatment-related or toxicologically relevant. The relative liver weight was increased in males at 16,000 ppm and in females at ≥ 2000 ppm (7.3-11.9%, $p \leq 0.05$ or 0.01). The liver weight increases, in conjunction with the histopathological liver changes, serum GGT increase in males, and demonstration (in supplementary study MRID 43864246) that hepatic cell proliferation was occurring in 16,000 ppm males (1140 mg/kg/day) suggest

8000 and 16,000 ppm on day 89 (about a 5-fold increase, $p \leq 0.01$). The only histopathological finding was a minor change in the amount and/or distribution of fat in hepatocytes (all dose groups, both sexes); it is unclear whether this effect is treatment-related or toxicologically relevant. The relative liver weight was increased in males at 16,000 ppm and in females at ≥ 2000 ppm (7.3-11.9%, $p \leq 0.05$ or 0.01). These liver weight increases were not considered toxicological significant.

Under the conditions of this study, the LOEL for male rats is 8000 ppm (577 mg/kg/day) based on elevated serum GGT (consistent with results seen in other studies); a LOEL was not established in females. The NOEL for males is 2000 ppm (146 mg/kg/day) and for females is 16000 ppm (1374 mg/kg/day.)

This subchronic toxicity study is classified as acceptable, and satisfies the guideline requirement for a subchronic oral study (82-1(a)) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided. With respect to the GLP statement, the study meets the requirements for 40 CFR 160 but differs in that it was conducted in accordance with the GLP-Provisions of the "Chemikaliengesetz" (Chemical ACT; Bundesgesetzblatt 1990, Teil I, 22.03.90; FR Germany) and with the "OECD Principles of Good Laboratory Practice" (Paris, 1981).

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Reg. No. 242 009

Description: beige powder
Lot/Batch #: test substance no. 90/577, batch no. N 21
Purity: 98.7% (w/w)
Stability of compound: stable at room temperature at least 32 days
CAS #: 143390-89-0

2. Vehicle and/or positive control

none

3. Test animals

Species: rat
Strain: Wistar Chbb:THOM(SPF)
Age and weight at study initiation: 42 days old; males: 167-192 g; females: 130-153 g
Source: Dr. Karl Thomae GmbH, Biberach/Riss, FRG
Housing: animals were housed singly in type DK III stainless steel wire cages with a floor area of about 800 cm^2

Diet: Animals were fed the ground KLIBA maintenance diet rat/mouse/hamster, 343 meal (supplied by KLINGENTALMÜHLE AG, Kaiseraugst, Switzerland) ad libitum.
Water: Drinking water was available ad libitum
Environmental conditions:
Temperature: 20-24 °C
Humidity: 30-70%
Air changes: not specified
Photoperiod: 12 hours light per 24 hour period
Acclimation period: 9 days

B. STUDY DESIGN

1. In life dates

start: October 10, 1990; end: January 11, 1991

2. Animal assignment

Animals were assigned randomly, based on their weights, to the test groups in Table 1.

TABLE 1: Study design

Test Group	Conc. in Diet (ppm)	Mean Dose to Animal (mg/kg/day)[1]		Number of Animals	
		Male	Female	Male	Female
0 (Control)	0 (Control)	0	0	10	10
1	500	36	43	10	10
2	2000	146	172	10	10
3	8000	577	672	10	10
4	16,000	1170	1374	10	10

Data taken from p. 36, MRID 43864245.
[1]Values calculated as time-weighted averages from the consumption and body weight gain data.

3. Diet preparation and analysis

Diet was prepared every three weeks by mixing appropriate amounts of test substance with ground KLIBA maintenance diet rat/mouse/hamster, 343 meal, and was stored at room temperature. The stability of the test substance over 32 days at room temperature was established in a previous experiment using a 50 mg/kg sample. The concentrations of all the test doses were sampled shortly after the beginning and before the end of the 3-month experimental period. The homogeneity at 500 ppm and 16,000 ppm was sampled near the beginning of the 3-month treatment period (6 samples at each concentration).

Results -
Homogeneity Analysis: 93.6-101% at 500 ppm; 95.6-103% at 16,000 ppm

Stability Analysis: At day 10, 101-102% of initial value; at day 32 97.0-99.1% of initial value

Concentration Analysis: 500 ppm: 93.6-104%; 2000 ppm: 92.3-93.3%; 8000 ppm: 91.4-100.2%; 16,000 ppm: 93.7-103%

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. Statistics

A parametric one-way ANOVA and Dunnett's test (two-sided) were used to make simultaneous comparisons of the test groups with the control group for the following parameters: body weight, body weight change, absolute and relative organ weights, serum enzymes, blood chemistry, and all hematology parameters except the differential blood count. No statistical analyses were reported for the food consumption, food efficiency, test substance intake, differential blood count, or the incidence of gross or microscopic lesions. The statistical calculations were performed on the computer systems of the Department of Toxicology of BASF Aktiengesellschaft.

C. METHODS

1. Observations

Animals were inspected twice a day on Monday-Friday, and once a day on Saturdays, Sundays, and holidays for signs of toxicity and mortality.

2. Body weight

Animals were weighed before the start of the administration period, on day 0 (start of administration period), and once a week thereafter.

3. Food consumption and compound intake

Food consumption for each animal was determined and mean daily diet consumption was calculated as g food/kg body weight/day. Food efficiency (body weight gain in g/food consumption in g per 7 days X 100) and compound intake (mg/kg/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. Ophthalmoscopic examination

Eyes were examined 1 day before and 86 days after the start of the study in test groups 0 (control) and 4 (16,000 ppm)

5. Blood was collected from the retro orbital venous plexus of all surviving animals (10 animals/sex/group) for hematology and clinical analysis. Blood was collected in the morning of days 43 and 89 with no prior fasting or anesthesia. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpusc. volume (MCV)
x	Platelet count*	x	Reticulocyte count
x	Blood clotting measurements*		
x	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic studies based on Subdivision F Guidelines

b. Clinical chemistry

X	ELECTROLYTES	X	OTHER
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
x	Magnesium	x	Blood urea nitrogen*
x	Phosphorus*	x	Total Cholesterol
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
	ENZYMES	x	Total bilirubin
x	Alkaline phosphatase (ALK)	x	Total serum protein (TP)*
	Cholinesterase (ChE)	x	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
x	Serum alanine amino-transferase (also SGPT)*		
x	Serum aspartate amino-transferase (also SGOT)*		
x	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Required for subchronic studies based on Subdivision F Guidelines

6. Urinalysis*

Urinalysis was not performed - it is not required for subchronic studies based on Subdivision F Guidelines.

6

7. Sacrifice and pathology

All animals survived the treatment period and were sacrificed on schedule by decapitation under CO_2 anesthesia. They were all subjected to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
x	Tongue	x	Aorta*	x	Brain*
x	Salivary glands*	x	Heart*	x	Periph. nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)[T]
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	x	Spleen*	x	Eyes (optic n.)[T]
x	Jejunum*	x	Thymus*		
x	Ileum*				GLANDULAR
x	Cecum*		UROGENITAL	xx	Adrenal gland*
x	Colon*	xx	Kidneys*[+]	x	Lacrimal gland[T]
x	Rectum*	x	Urinary bladder*	x	Mammary gland[T]
x	Liver*[+]	xx	Testes*[+]	x	Parathyroids*
x	Gall bladder*	x	Epididymides	x	Thyroids*
	Pancreas*	x	Prostate		
x		x	Seminal vesicle		OTHER
	RESPIRATORY	x	Ovaries	x	Bone
	Trachea*	x	Uterus*	x	Skeletal muscle
x	Lung*	x	Vagina	x	Skin
x	Nose			x	All gross lesions and masses*
	Pharynx				
	Larynx				

* Required for subchronic studies based on Subdivision F Guidelines
[+] Organ weight required in subchronic and chronic studies.
T = required only when toxicity or target organ

II. RESULTS

A. OBSERVATIONS

1. Toxicity

There were no observable effects on the animals due to compound administration.

2. Mortality

All animals survived to study termination.

B. BODY WEIGHT AND WEIGHT GAIN

There were statistically significant decreases ($p \leq 0.05$ or 0.01) in the body weight and body weight gains of 8000 ppm males (from day 28 to study termination), and of 16,000 ppm males (days 35, 56, and 77). The body weight decreases were relatively small (6.6-9.5% at 8000 ppm; 6.9-7.7% at 16,000 ppm). The body weight gains decreased

in parallel with the body weight decreases in the males, being up to 15.2% lower than controls at 8000 ppm and up to 12.9% lower at 16,000 ppm. There were no statistically significant body weight effects on females at any dose. The results are shown in Table 2.

TABLE 2. Group mean body weights and final body weight gains (g) in male rats fed Reg. No. 242 009 for 91 days[1]

Day of study	Exposure concentration (ppm)				
	0	500	2000	8000	16,000
0	183.8	182.8 (0.5%)	179.5 (2.3%)	181.9 (1.0%)	181.4 (1.3%)
14	287.1	286.8 (0.1%)	280.4 (2.3%)	274.0 (4.6%)	278.2 (3.1%)
28	352.3	351.8 (0.1%)	339.8 (3.5%)	329.2* (6.6%)	337.3 (4.3%)
42	400.5	400.1 (0.1%)	385.2 (3.8%)	368.5* (8.0%)	377.6 (5.7%)
56	441.5	437.1 (1.0%)	419.1 (5.1%)	400.4** (9.3%)	411.2* (6.9%)
77	484.7	479.4 (1.1%)	461.5 (4.8%)	439.7** (9.3%)	447.3* (7.7%)
91	493.8	491.0 (0.6%)	469.8 (4.9%)	448.8* (9.1%)	463.2 (6.2%)
Final Body Weight Gain	310.0	308.2 (0.6%)	290.3 (6.4%)	266.9* (13.9%)	281.9 (9.1%)

Data taken from Tables 5, 6, 9, and 10, pp. 51-52 and 55-56, MRID 43864245.
Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.
[1]Numbers in parenthesis are the percent decrease relative to untreated controls, calculated by the reviewer.

C. FOOD CONSUMPTION AND COMPOUND INTAKE

1. Food consumption

No effects on food consumption (g/animal/day) were seen in any group of animals.

2. Compound consumption

Animals were given the test compound in the diet, and its mean daily intake a time-weighted average (mg compound/kg/day) for both sexes is given in Table 1.

3. Food efficiency

There were no notable or consistent differences between the control and treated groups of either sex; statistical analysis was not performed. The weekly efficiency values varied widely during the last month of the study, both between and among the dose groups (large standard deviation).

D. OPHTHALMOSCOPIC EXAMINATION

There were no treatment-related findings.

E. BLOOD WORK

1. Hematology

No treatment-related effects were seen in either sex at any dose. There were transient increases in white blood cells (27%; $p \leq 0.01$) and in the MCHC (1.8%; $p \leq 0.05$) in high-dose females at day 43, both values being within 1.2% of controls at day 89.

2. Clinical Chemistry

Serum alanine aminotransferase (SGPT) was significantly decreased (17.2-29.6%; $p \leq 0.05$ or 0.01) in almost all dosed groups of both sexes compared to untreated controls at day 43 only. Alkaline phosphatase (AP) was also lower than controls in most dosed groups of both sexes (17.0-32.9%; $p \leq 0.05$ or 0.01), at both days 43 and 89. Additionally, in 8000 and 16,000 ppm males only, there was about a 28% decrease ($p \leq 0.05$) in aspartate aminotransferase (SGOT) at day 43, and about a 5-fold increase ($p \leq 0.01$) in gamma-glutamyl transferase (GGT) at day 89. These enzyme changes may be treatment-related, though the toxicological significance of decreased SGPT, AP, and SGOT is questionable because the changes were not clearly related to dose and/or were transient. Also, the pathological consequences of a minor decrease in enzyme levels is uncertain. The slight decrease in serum chloride concentration in 16,000 ppm females at day 43 (1.4%, $p \leq 0.05$) was likely incidental to treatment. These results are summarized below in Table 3.

TABLE 3: Clinical chemistry changes in rats given Reg. No. 242 009

Parameter	Day	Dose (ppm)				
		0	500	2000	8000	16,000
Males						
Alanine aminotransferase (SGPT) (microkatal/L)	43	1.16	0.96*	0.95*	0.82**	0.95*
	89	1.01	0.94	0.99	0.82	0.87
Aspartate aminotransferase (SGOT) (microkatal/L)	43	2.01	1.67	1.63	1.45*	1.46*
	89	2.51	2.03	2.14	1.68	1.81
Alkaline phosphatase (AP) (microkatal/L)	43	7.33	5.87**	6.00**	4.92**	5.60**
	89	5.37	4.42	4.61	3.76**	4.30*
Gamma-glutamyl transferase (nanokatal/L) (GGT)	43	6	15	23	28	37
	89	11	21	23	52**	60**
Females						
Alanine aminotransferase (SGPT) (microkatal/L)	43	1.08	0.95	0.83**	0.76**	0.82**
	89	0.84	0.86	0.74	0.81	0.80
Alkaline phosphatase (AP) (microkatal/L)	43	5.46	4.80	4.02**	4.23**	4.53*
	89	3.89	3.42	2.71**	3.02**	3.09**

Data taken from pages 93-96, MRID 43864245.
Significantly different from control: *$p \leq 0.05$; **$p \leq 0.01$.

F. URINALYSIS

Urinalysis was neither required nor performed in the study.

G. SACRIFICE AND PATHOLOGY

1. Organ weight

Compared to untreated controls, the relative weight of the liver (relative to body weight) was statistically significantly increased in 16,000 ppm males and in 2000, 8000, and 16,000 ppm females (7.3-11.9%, $p \leq 0.05$ or 0.01). The increase in females was not definitively dose-related. Kidney weight was also affected in both sexes, a relative increase occurring in males at 2000 ppm and above (8.8-12.8%, $p \leq 0.05$ or 0.01), and an absolute weight decrease of 9.0% ($p \leq 0.05$) was seen only in 500 ppm females. The relative weight of the adrenals was also increased in 8000 ppm males (23.6%, $p \leq 0.01$). Of these organ weight changes, the relative liver weight increases are likely the most toxicologically significant because they are correlated with liver histopathological changes in both sexes and increased SGGT in males. The small magnitude of the other organ weight changes and their lack of a clear dose-response or histopathological correlates suggest they were not biologically important. The results are shown in Table 4.

TABLE 4: Organ weights, absolute and relative (to total body weight) of rats given Reg. No. 242 009 for 2 years[1]

Organ and Terminal Body Weight	Dose (ppm)				
	0	500	2000	8000	16,000
Males					
Body weight(g)	469.15	462.60	439.28	416.49**(11.2)	434.03
Liver:					
Absolute (g)	16.081	16.767	15.568	15.349	16.287
Relative (%)	3.425	3.616	3.542	3.679	3.772* (10.1)
Kidneys:					
Absolute (g)	2.971	3.096	3.025	2.975	3.023
Relative (%)	0.634	0.669	0.690* (8.8)	0.715** (12.8)	0.700**(10.4)
Adrenal glands:					
Absolute (g)	81.6	78.4	82.3	85.6	85.0
Relative (%)	0.017	0.017	0.019	0.021* (23.6)	0.020
Females					
Body weight(g)	243.23	241.11	237.52	232.05	228.37
Liver:					
Absolute (g)	7.264	7.299	7.769	7.435	7.642
Relative (%)	2.991	3.028	3.276**(9.5)	3.209** (7.3)	3.348**(11.9)
Kidneys:					
Absolute (g)	1.970	1.792*(9.0)	1.922	1.837	1.826
Relative (%)	0.811	0.745	0.813	0.796	0.800

Data taken from pages 271-274, MRID 43864245.
Significantly different from control: *p ≤ 0.05; **p ≤ 0.01.
[1]Numbers in parenthesis are the percent change relative to untreated controls calculated by the reviewer.

2. Gross pathology

There were no treatment-related findings. (The incidence of any observed lesion never exceeded 1 per dose group.)

3. Microscopic pathology

a) Non-neoplastic - The most notable histopathological finding was a decrease in the grade of diffuse fatty infiltration of the hepatocytes in both male and female rats. The proportion of rats having slight fatty infiltration (grade 2) decreased compared to the number having minimal fat infiltration (grade 1) in a dose-dependent manner. Females also had a marked decrease in the total incidence of fatty infiltration. These changes appear to be treatment-related, and, in concert with the increased relative liver weight (both sexes) and SGGT (males) indicate that the liver is a target organ in both sexes of rats. This conclusion is also supported by the results of the hepatic cell proliferation assay in males (MRID 43864246;

summarized in the Appendix). The toxicological significance of the changes in liver fatty infiltration is uncertain but probably minor. The histopathology results are shown in Table 5.

TABLE 5: Incidence of microscopic changes found in rats given Reg. No. 242 009

Diffuse fatty hepatocyte infiltration	Dose (ppm)				
	0	500	2000	8000	16,000
Males					
Total incidence	9/10	10/10	8/10	8/10	8/10
Grade 1 (minimal)	4/10	6/10	6/10	6/10	7/10
Grade 2 (slight)	5/10	4/10	2/10	2/10	1/10
Females					
Total incidence	9/10	9/10	6/10	3/10	2/10
Grade 1 (minimal)	8/10	9/10	6/10	3/10	2/10
Grade 2 (slight)	1/10	-	-	-	-

Data taken from pages 281-282, MRID 43864245.

b) Neoplastic - There were no neoplastic findings.

III. DISCUSSION

A. DISCUSSION

In a subchronic toxicity study (MRID 43864245) Reg. No. 242 009 was administered to 10 Wistar rats/sex/dose in the feed at doses of 0, 500, 2000, 8000, and 16,000 ppm (mean compound intake in males was 0, 36, 146, 577, and 1170 mg/kg/day, respectively, and in females was 0, 43, 172, 672, 1374 mg/kg/day, respectively). Food and water were provided *ad libitum*. The rats were examined once or twice daily for signs of toxicity and mortality, and were weighed weekly. Blood was collected on days 43 and 89 to measure hematology and clinical chemistry parameters.

All the animals survived to study termination. There were minor, statistically significant though not dose-related decreases in the body weights (≤ 9.5%) and body weight gains (≤ 15.2%) of 8000 and 16,000 ppm males. These were not accompanied by effects on food consumption or food efficiency. The transient hematological alterations (white blood cell and MCHC decreases) in 16,000 ppm females were probably incidental to treatment.

The levels of serum SGPT and alkaline phosphatase (AP) were 17-33% lower than controls in most dose groups of both sexes. Similar dose-independent decreases were also

seen in a 2-year chronic feeding rat study (MRID 43864247), and the origins and pathological significance of these decreases was investigated (by D.W. Moss, London, U.K.; pp. 419-441). It was concluded that the SGPT and AP decreases were not toxicologically relevant and were probably due to a "slight alteration in food resorption in the treated animals" based on the lack of dose-response, the reversibility of the changes, and the lack of effect on body weight, development, and food consumption. The transient decrease in SGOT in 8000 and 16,000 ppm males (about 28%, day 43 only) was not clearly dose-related, and not toxicologically significant. Gamma-glutamyl transferase (GGT) was elevated in males in a time and dose-dependent manner, reaching statistical significance at 8000 and 16,000 ppm on day 89 (about a 5-fold increase). The GGT increase indicates that the liver may be a target organ in males, which was supported by the increased relative liver weight at 16000 ppm. While the increased relative liver weight in females at ≥ 2000 ppm may suggest that the liver is also a target organ in females, the weight increase was not correlated with dose (i.e. liver weights were slightly greater at 2000 ppm than at 8000 ppm) and therefore toxicological significance could not be established. The minor changes in hepatocyte fatty infiltration in males and females are consistent with the liver being a target organ, although their toxicological significance is unclear. All the pathological changes were relatively minor and did not appear to compromise the health of the animals in the course of the 3-month study.

The only other statistically significant effects in males were a small increase in the relative weight of the kidneys (8.8-12.8%) and adrenal glands (23.6%) at one or more doses, neither increase being clearly dose-related. It is unknown whether these changes were compound-related or artefacts of the slightly decreased animal body weights (brain weights were not determined), but the lack of histopathological correlates indicates they were not toxicologically significant. In females, there was a small (9.0%) decrease in the absolute weight of the kidneys at 500 ppm, which was likely incidental to treatment.

Based on serum GGT level increases, the LOEL for male rats is 8000 ppm (577 mg/kg/day) under the conditions of this study. The LOEL for female rats is not established. The NOEL for males is 2000 ppm (146 mg/kg/day) and for females is 16000 ppm (1374 mg/kg/day).

In a separate study (MRID 43864246; summarized in the Appendix), the effect of Reg. No. 242 009 on hepatic cell proliferation was investigated. (The motivation for this study was not given, presumably it was to confirm the

liver as a target organ and to explore the possible mechanism of action of the test compound.) In this study, 5 male rats/dose were given 0, 200, or 16,000 ppm (0, 15, 1140 mg/kg/day, respectively) in the feed for 3 weeks, during the last week also being given bromodeoxyuridine from subcutaneously implanted osmotic minipumps. No treatment-related effects were seen (body weight, food consumption, clinical observations, liver weight, gross or microscopic lesions) except for a statistically significant increase (2 to 3-fold) in cell proliferation in the hepatic lobules of the 16,000 ppm group. This result is consistent with a 2-year chronic feeding rat study (MRID 43864247), where hepatocellular carcinomas developed and numerous liver-related toxicological parameters were altered. These two studies taken together (chronic feeding and 3-week cell proliferation) suggest that the minor liver-related alterations in the 3-month study were precursors of effects not yet detectable during that period, and are supportive of the liver being a target organ.

B. STUDY DEFICIENCIES

There were no major deficiencies that would alter the interpretation or classification of this study as being acceptable. Minor deficiencies include failure to statistically analyze the food consumption, food efficiency, test substance intake, differential blood count, and the incidence of gross and microscopic lesions. It would have been helpful if the level of plasma glutamate dehydrogenase were assayed as there were indications that the test compound affected the liver.